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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/042,711	BROWN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39,43,49-51,58,62,63,69,73 and 74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,43,49-51,58,63,69 and 74* is/are rejected.

7)☒ Claim(s) *62 and 73* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 22, 2010 (hereinafter referred to as "the response") has been entered. Claims 39, 49, 58, 62, 69, and 73 have been amended. Claims 60, 71, and 72 have been cancelled.

Accordingly, Claims 39, 43, 49-51, 58, 62, 63, 69, 73, and 74 remain pending in the instant application.

The elected invention is drawn to a method for developing a therapeutic procedure in a model animal system (*in vivo* testing of a procedure).

Claims 39, 43, 49-51, 58, 62, 63, 69, 73 and 74 are examined herein.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 22, 2010 has been entered.

Priority

Applicant's claim for domestic priority under 35 U.S.C. § 120 is acknowledged. However, the non-provisional application 08/876,635 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for Claims 39, 43, 49-51, 58, 62, 63, 69, 73 and 74 of this application. The earlier-filed application does not disclose an animal model as recited in the instantly claimed methods.

Accordingly, the effective filing date of the instant application is July 16, 1999, the filing date of Application No. 09/356,293.

Applicants did not address this issue in the response, nor in the prior response, as noted in the Office action of 7/22/09 (page 3).

Claim Objections

Claim 62 and 73 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of the claim from which it depends (Claims 58 and 69, respectively). Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. See MPEP § 608.01(n). The independent claims, Claims 58 and 69, already exclude the subject matter of Claims 62 and 73 (i.e., wherein the human viral pathogen is HBV). Claims 58 and 69 already recite the limitation "wherein said pathogen is HCV, HIV-1 or HIV-2" thereby excluding HBV. Accordingly, Claims 62 and 73 have not been further treated on the merits.

Appropriate correction is required.

Double Patenting

Applicant is advised that should Claim 51 be found allowable, Claim 69 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Claim 69 has been amended to narrow the scope of the human viral pathogen so that the claim is now a duplicate of Claim 51. The method steps are now identical. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant is advised that should Claim 58 be found allowable, Claim 69 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Claim 69 has been amended to narrow the scope of the human viral pathogen so that the claim is now a duplicate of Claim 58. The method steps are now identical. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant is advised that should Claim 51 be found allowable, Claim 58 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Claim 58 has been amended to narrow the scope of the human viral pathogen so that the claim is now a duplicate of Claim 51. The method steps are now identical. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant is advised that should Claim 63 be found allowable, Claim 74 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Claim 74 depends from Claim 69 which has been amended to narrow the scope of the human viral pathogen so that Claim 69 is now a duplicate of Claim 58, from which Claim 63 depends. Claim 74 recites the same further limitation as Claim 63. Accordingly, the method steps of Claims 63 and 74 are now identical. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 39, 43, 49-51, 58, 63, 69, and 74 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for developing a therapeutic procedure. The claimed method involves infecting *Tupaia belangeri* with a human viral pathogen, wherein said pathogen is HCV, HIV-1, or HIV-2, carrying out a potential therapeutic procedure on the infected animal, and evaluating the effect of the therapeutic procedure on disease manifestations caused by the human viral pathogen in the infected animal. Certain claims recite the evaluation of specific disease manifestations, including inflammation, fibrosis, induced autoimmunity, apoptosis, or a combination thereof. Thus, a variety of indicators of hepatic disease may be evaluated, as recited in the claims.

The specification fails to provide a written description of a *Tupaia belangeri* infected with HCV, HIV-1 or HIV-2 and having a disease phenotype marked by inflammation, fibrosis, induced autoimmunity, or apoptosis, or any other disease phenotype, such that the infected animal would model the human infection and disease sequelae. Animal models of infectious disease are notoriously unpredictable for reasons of record, and therefore one of skill in the art would not know if a *Tupaia belangeri* infected with HCV, HIV-1 or HIV-2 would exhibit disease characteristics analogous to the disease characteristics observed in humans. The phenotype of an HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri* is not known and is not described. Claims that recite evaluation of specific parameters, such as inflammation, fibrosis, induced autoimmunity, apoptosis, or a combination thereof, require an infected tupaia that has a phenotype of inflammation, fibrosis, induced autoimmunity, apoptosis, or combinations thereof, but the specification does not describe such an animal. Because disease phenotypes

are unpredictable in animal model systems, extensive characterization of the animal model is required before it can be used in a screening protocol to identify therapeutic procedures. Because disease manifestations are not predictable, the disease characteristics of the infected animal must be determined experimentally. However, the instant specification provides no description of the phenotype of an HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri*, let alone a phenotype suitable for evaluation of the claim-designated parameters as indicators of viral disease caused by HCV, HIV-1, or HIV-2.

The evidence of record shows that animal models of human infectious disease are notoriously unpredictable (see Lewis et al., 1995). Numerous attempts to produce or identify a suitable animal model for HIV infection have met with limited success (Lewis et al., 1995). The prior art shows that macaques, baboons, chimpanzees, pig-tailed macaques, and gibbons are susceptible to infection with HIV. Thus, the nonhuman host range is extremely limited. Moreover, the pathogenesis varies substantially from species to species. Lewis et al. (1995) discuss the many problems that exist with regard to the disease characteristics displayed by the best animal models for HIV infection. Furthermore, animal models require extensive characterization before they can be used in pre-clinical testing (see Lewis et al., page 149, column 1, paragraph 1). Intensive effort has been applied to developing animal models of HIV and other viral diseases with extremely limited success.

The instant specification only discloses two model systems; one *in vivo* (HBV-infected *Tupaia belangeri*) and one *in vitro* (HIV-1-infected *Tupaia belangeri* cells). *Tupaia belangeri* were shown to be susceptible to infection by HBV and their peripheral blood lymphocytes (PBLs) to infection by HIV-1 in culture. No other human viral pathogens were examined for their capacity to infect *Tupaia belangeri in vivo*. Furthermore, given the open claim language, genetic modification may be used to develop a *Tupaia belangeri* strain that is rendered susceptible to infection by HIV-1 or HIV-2, or to develop a genetically-modified strain that is rendered a more robust host for efficient infection with HCV. The claims encompass genetically modified *Tupaia belangeri* animals, but the specification does not disclose any

genetic modifications that could be made to render an individual *Tupaia belangeri* susceptible to infection by one of the human viral pathogens recited in the claims or to produce a model that more accurately reflects the disease manifestations observed in infected humans. In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. In this case, only one animal model (the HBV-infected *Tupaia belangeri*) has been tested to investigate possible disease manifestations that may be exhibited over the course of an infection. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, no other embodiments have been sufficiently described by relevant identifying characteristics. This limited information regarding the claimed embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the *Tupaia belangeri* animal models required by the claims, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed methods.

With regard to the claimed methods for developing a therapeutic procedure, adequate written description is not provided in the as-filed specification. The as-filed specification does not describe a method for evaluating a therapeutic procedure with the steps set forth in the present claims. Even as relates to the disclosed *Tupaia belangeri* models, no *in vivo* screening methods are disclosed as such. With regard to HIV, only an *in vitro* model system is disclosed, and there is no contemplation of carrying out the steps of the presently claimed method using a *Tupaia belangeri* infected with HIV-1 or HIV-2. The absence of any written description of screening methods as claimed cannot be remedied by oral tolerization experiments carried out with HBV-infected *Tupaia belangeri*, as the claims are much broader in scope than what is described in that experiment. Thus it is concluded that the written description requirement is not satisfied for the claimed methods.

While the skilled artisan would know the disease symptoms displayed by humans for any given human viral pathogen, the artisan would not know the disease symptoms displayed by any given *Tupaia belangeri* animal in response to an infection with HCV, HIV-1, or HIV-2. As the art of record shows, different animals exhibit different symptoms and most do not exhibit the same symptoms seen in humans. As Lewis et al. shows, animal models require extensive characterization before they can be used in pre-clinical testing and the instant specification provides **no** information with regard to disease phenotypes in *Tupaia belangeri* for human viral pathogens other than HBV. Given the unpredictability in the art, for reasons of record, the specification provides no guidance as to what symptoms would be exhibited by a *Tupaia belangeri* infected with HCV, HIV-1, or HIV-2. While the prior art provides some guidance with regard to the disease manifestations observed in HCV-infected *Tupaia belangeri*, the instant specification does not provide a written description of an HCV-infected *Tupaia belangeri* or for a method of screening potential therapeutice procedures by carrying out those procedures on an HCV-infected *Tupaia belangeri*.

At page 7 of the response, Applicants argue that there is a strong presumption that an adequate written description of the claimed invention is present when an application is filed and that it is the Patent Office's burden to overcome this presumption and establish that one skilled in the art would not recognize that the inventor had possession of the claimed invention because, for example, the recited elements are not conventional in the art or known to one of ordinary skill in the art and are not described in the specification. However, it is the role of the specification to describe the novel features of the invention in order to demonstrate possession of the invention. Here, it does not, because *Tupaia belangeri* infected with the claim-designated human viral pathogens and suitable for evaluation of the disease manifestations that result from those infections are not described. There is no description of an HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri*, let alone a phenotype suitable for evaluation of the claim-designated parameters as indicators of viral disease caused by HCV, HIV-1, or HIV-2.

At page 7 of the response, Applicants note that the claims have been amended to narrow the scope to the use of HCV, HIV-1, or HIV-2, as well as to the use of *Tupaia belangeri*. While the narrowed scope is acknowledged, the specification fails to provide an adequate written description for methods that involve evaluating disease manifestations that have not been described in *Tupaia belangeri* infected with the claim-designated human viral pathogens. There is no description at all of any disease manifestations in *Tupaia belangeri* infected with HCV, HIV-1, or HIV-2. Without a written description, the skilled artisan would not find that Applicants were in possession of HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri* that exhibit disease characteristics analogous to those seen in humans, such that the infected animal would adequately model the human disease.

At page 8, paragraph 2 of the response, Applicants assert that HIV-2 can utilize the same receptors as HIV-1 such that successful infection by HIV-1 makes it highly likely that HIV-2 will also share this same characteristic. However, even if HIV-2 was able to infect the lymphocytes of *Tupaia belangeri*, which there is no evidence for, there is no degree of predictability that this species would adequately model the human disease once infected. Susceptibility to infection is only the first obstacle to be overcome in generating an animal model that exhibits one or more hallmarks of a human disease. Thus, in the absence of a description of infected animals that exhibit analogous disease manifestations, one of skill in the art would not find that Applicants were in possession of an animal model suitable for the therapeutic screening protocol claimed.

At page 8, paragraph 2 of the response, Applicants note that it was known in the art at the time of filing that HCV can infect *Tupaia*. Applicants cite Xie et al. (1998, Virology 244: 513-520) for providing this teaching. Applicants note, however, that it was <u>not known</u> whether HCV infection of *Tupaia* duplicated secondary manifestations that are the hallmark of human infection by both HBV and HCV. Applicants allege that the parallels between the HBV and HCV self-destructive immune responses in humans make it very likely that this would continue to be paralleled in *Tupaia* infections and, as such, "it

has been predicted that HCV would have secondary disease manifestations." However, there is no evidence that HCV-infected *Tupaia belangeri* would exhibit the particular disease manifestations recited in the claims, including a phenotype of inflammation, fibrosis, induced autoimmunity, apoptosis, or combinations thereof.

At page 8, paragraph 3 of the response, Applicants assert that Example 2 specifically describes a therapeutic process, i.e. oral tolerization, that was developed using *Tupaia* as an animal model. However, the model system used in Example 2 was **HBV**-infected *Tupaia belangeri*, which falls outside the scope of the claims. Thus, Example 2 does not provide a written description for HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri* that exhibit disease characteristics analogous to those seen in humans, such that the infected animal would adequately model the human disease. Applicants allege that the present application teaches the use of an animal model that would be suitable for procedures to be developed by the user and that once given this tool, one skilled in the art would have the ability to use this tool. However, the instant specification would not put one of skill in the art in possession of an HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri* that exhibits disease characteristics analogous to those seen in humans, and therefore the skilled artisan would not be in possession of the tool that Applicants refer to. The missing element, required for the claimed method to be carried out, is the animal exhibiting the hoped-for disease manifestations that correlate to the human disease, but animals having the necessary characteristics have not been described and the skilled artisan cannot predict the phenotype of HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri*, given the unpredictability in the art of animal models, for reasons of record.

Enablement

Claims 39, 43, 49-51, 58, 63, 69, and 74 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of *Tupaia belangeri* infected with HBV in the

method for developing a therapeutic procedure, wherein the effect of said therapeutic procedure on clinical manifestations are evaluated by measuring serum alanine aminotransferase (ALT) levels, does not reasonably provide enablement for the other human viral pathogens listed (HCV, HIV-1 or HIV-2) or for methods that involve the measurement of other parameters as indicators of disease manifestations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for developing a therapeutic procedure, wherein the method involves evaluating a variety of indicators of hepatic disease as recited in the claims. The claimed method involves infecting *Tupaia belangeri* with a human viral pathogen, wherein said pathogen is HCV, HIV-1 or HIV-2, carrying out a potential therapeutic procedure on the infected animal, and evaluating the effect of the therapeutic procedure on disease manifestations caused by the human viral pathogen in the infected animal. Certain claims recite the evaluation of specific disease manifestations, including inflammation, fibrosis, induced autoimmunity, apoptosis, or a combination thereof. Thus, a variety of indicators of hepatic disease may be evaluated, as recited in the claims.

The specification fails to provide an enabling disclosure for the use of a *Tupaia belangeri* infected with HCV, HIV-1 or HIV-2 and having a disease phenotype marked by inflammation, fibrosis, induced autoimmunity, or apoptosis, or any other disease phenotype, such that the infected animal would model the human infection and disease sequelae. Animal models of infectious disease are notoriously unpredictable for reasons of record, and therefore one of skill in the art would not know *a priori* if a *Tupaia belangeri* infected with HCV, HIV-1 or HIV-2 would exhibit disease characteristics analogous to the disease characteristics observed in humans. The phenotype of an HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri* is unpredictable. Claims that recite evaluation of specific parameters, such as inflammation, fibrosis, induced autoimmunity, apoptosis, or a combination thereof, require an infected *Tupaia belangeri* individual that has a phenotype of inflammation, fibrosis, induced autoimmunity,

apoptosis, or combinations thereof, but the specification does not describe such an animal. Because disease phenotypes are unpredictable in animal model systems, extensive characterization of the animal model is required before it can be used in a screening protocol to identify therapeutic procedures. Because disease manifestations are not predictable, the disease characteristics of the infected animal must be determined experimentally. However, the instant specification provides no guidance regarding the phenotype of an HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri*, let alone a phenotype suitable for evaluation of the claim-designated parameters as indicators of viral disease caused by HCV, HIV-1, or HIV-2.

The instant specification only discloses two model systems; one *in vivo* (HBV-infected *Tupaia belangeri*) and one *in vitro* (HIV-1-infected *Tupaia belangeri* cells). *Tupaia belangeri* were shown to be susceptible to infection by HBV and their peripheral blood lymphocytes (PBLs) to infection by HIV-1 in culture. No other human viral pathogens were examined for their capacity to infect *Tupaia belangeri in vivo*. Furthermore, given the open claim language, genetic modification may be used to develop a *Tupaia belangeri* strain that is rendered susceptible to infection by HIV-1 or HIV-2, or to develop a genetically-modified strain that is rendered a more robust host for efficient infection with HCV. The claims encompass genetically modified *Tupaia belangeri* animals, but the specification does not disclose any genetic modifications that could be made to render an individual *Tupaia belangeri* susceptible to infection by one of the human viral pathogens recited in the claims or to produce a model that more accurately reflects the disease manifestations observed in infected humans. Animal models of human infectious disease are notoriously unpredictable as evidenced by the numerous attempts to produce or identify a suitable animal model for HIV infection (see Lewis et al., 1995). Lewis et al. (1995) discuss the many problems that exist with regard to the disease characteristics displayed by the best animal models for HIV infection. None of the animal models exhibit the ideal characteristics as outlined in Box 1, page 144.

Thus, despite an enormous amount of data on the HIV virus and its role in causing AIDS, and despite intense efforts to generate an adequate animal model, significant deficiencies remain.

Given the lack of specific guidance in the specification with regard to HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri*, the limited working examples disclosed, and the unpredictability in the art for developing animal models of human infectious diseases, one skilled in the art would have been required to engage in undue experimentation to produce the claimed *Tupaia belangeri* animal models over the full scope in order to use the animal models in the claimed methods.

At page 6 of the response, Applicants note that the claims have been amended to narrow the scope of the animal to *Tupaia belangeri* and to narrow the scope of the pathogen to HCV, HIV-1, or HIV-2. Applicants assert that it was known in 1998 that HCV could infect *Tupaia*. Applicants cite Xie et al. (1998, Virology 244: 513-520) for providing this teaching. Applicants further assert that the specification clearly describes methods for determining susceptibility to HBV and also describes support for HIV in the methods of the invention. Applicants conclude that methods to evaluate susceptibility of *Tupaia belangeri* to infection by a given viral pathogen are well understood by one skilled in the art. Applicants assert that the same receptors "are present on both HIV 1 and HIV 2." Applicants cite Hill et al. (1997) for this teaching. Applicants conclude that successful infection by HIV-1 therefore indicates that HIV-2 will also be capable of infecting *Tupaia belangeri*. However, as noted above, there is no evidence that HCV-infected *Tupaia belangeri* would exhibit the particular disease manifestations recited in the claims, including a phenotype of inflammation, fibrosis, induced autoimmunity, apoptosis, or combinations thereof. As further noted above, even if HIV-1 and HIV-2 were able to infect *Tupaia belangeri in vivo*, which there is no evidence for with regard to HIV-2, and limited evidence with regard to HIV-1, there is no degree of predictability that this animal species would adequately model the human disease once infected. Susceptibility to infection is only the first obstacle to be overcome in generating an animal model that exhibits one or more hallmarks of a human disease. Thus, in the absence of specific guidance

for producing infected animals that exhibit analogous disease manifestations, one of skill in the art would not be able to carry out the claimed method without undue experimentation.

At page 6, paragraph 3 of the response, Applicants allege that the claims are fully enabled and that "one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." However, the pending claims remain broader than the indicated scope of enablement and Applicants have not provided adequate arguments or evidence with regard to this broader scope. In particular, there is no evidence that the disease symptoms observed in humans would also be observed in HCV-, HIV-1-, or HIV-2-infected *Tupaia belangeri*, and the evidence of record shows that animal models of human infectious disease are notoriously unpredictable. Given the broad scope of the claims, which includes genetic manipulations to enhance viral susceptibility, and the limited guidance in the specification, the skilled artisan would have been required to engage in undue experimentation to practice the claimed methods over the full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xie et al. (1998, Virology 244: 513-520).

Xie et al. (1998) provide the first report of susceptibility of *Tupaia belangeri* to hepatitis C virus (page 513, column 2). The reference notes that "[t]hese animals may serve as an *in vivo* system for culturing HCV and addressing the pathophysiological and therapeutic issues of HCV infection" (abstract, last sentence). The reference teaches that HCV infection was confirmed by detection of HCV RNA and anti-HCV antibodies in the blood. At 50 weeks post-inoculation, liver biopsies from infected tupaias showed ballooning degeneration of hepatocytes together with multinucleated liver cells and macrovesicular or focal necrosis with inflammatory infiltrate in some (page 514, column 2). With regard to disease manifestations, the reference discloses that serum levels of alanine aminotransferase (ALT), a well-known marker of liver damage, were significantly elevated in HCV-inoculated tupaias (page 517, column 2, paragraph 2). The reference further notes that peak ALT levels occurred, in most of the animals, between the 8^{th} and 12^{th} weeks, which is the approximate time of occurrence of the transaminase peak in the acute phase of experimental HCV infection in chimpanzees (page 517, column 2, paragraph 2). Therefore, given the authors' suggestion to use HCV-infected *Tupaia belangeri* to develop therapies, it would have been obvious to one of skill in the art to infect a Tupaia belangeri with HCV, carry out a potential therapeutic procedure on the infected tupaia, and evaluate the effect of the therapeutic procedure on serum ALT levels to determine if the procedure is therapeutic. Since elevated ALT levels are a marker of liver damage, lower levels of ALT, as compared to ALT levels in untreated control animals, would indicate that the procedure is therapeutic. A reasonable expectation of success would have been anticipated because serum levels of ALT are a well-known marker of liver damage and screening methods that employ animal model systems to identify therapies are well known in the art and are the

preferred means for pre-clinical testing. In fact, the instant specification admits that the release of ALT from lysed hepatocytes into the plasma is a marker of hepatocyte death and indicative of liver injury. In particular, the specification notes that ALT levels in plasma are a standard measure of hepatocyte death and injury (paragraph bridging pages 13-14).

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632